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(54) Title: RESERVOIR DEVICE FOR INTRAOCULAR DRUG DELIVERY

(57) Abstract: A delivery device that allows for the sustained release of an agent, particularly useful for the sustained release of a therapeutic agent to limited access regions, such as the posterior chamber of the eye and inner ear. The delivery device is minimally invasive, refillable and may be easily fixed to the treatment area. The delivery device includes a hollow body with an inlet port at its proximal end for insertion of the agent, a reservoir for holding the agent and a delivery mechanism for the sustained delivery of the agent from the reservoir to the patient.

RESERVOIR DEVICE FOR INTRAOCULAR DRUG DELIVERY

The present application claims the benefit of U.S. provisional application number 60/297,499 filed June 12, 2001, which is incorporated by reference herein in its entirety.

5 FIELD OF THE INVENTION

The present invention relates to improved delivery devices and methods of use. More particularly, the present invention relates to minimally invasive, refillable, sustained release delivery devices particularly suitable for the delivery of therapeutic agents to limited access regions, such as the posterior chamber of the eye.

10

BACKGROUND OF THE INVENTION

The delivery of drugs to the eye presents many challenges. The ocular absorption of systemically administered pharmacologic agents is limited by the blood ocular barrier, namely the tight junctions of the retinal pigment epithelium and vascular endothelial cells. High systemic doses can penetrate this blood ocular barrier in relatively small amounts, but expose the patient to the risk of systemic toxicity. Topical delivery of drugs often results in limited ocular absorption due to the complex hydrophobic/hydrophilic properties of the cornea and sclera. Additionally, topical agents are mechanically removed by the blink mechanism such that only approximately 15% of a single drop is absorbed. Diffusion of topically administered drugs to the posterior chamber occurs, but often at sub-therapeutic levels. Intravitreal injection of drugs is an effective means of delivering a drug to the posterior segment in high concentrations. However, these repeated intraocular injections carry the risk of infection, hemorrhage and retinal detachment. Patients also find this procedure somewhat difficult to endure.

Local sustained delivery of therapeutics to the posterior chamber is critical in managing several chronic diseases of the eye. To address this need, several drug

delivery devices have been developed for intraocular insertion into the vitreous region of the eye.

U.S. Patent No. 4,300,557, for example, describes an intraocular implant in the
5 form of a silicone capsule which can be filled with a drug to be delivered. The
capsule is inserted in the vitreous region of the eye by making an incision in the eye,
inserting the capsule and closing the incision. The capsule remains in place for a
period of time and may be removed by making a second surgical incision into the eye
and retrieving the device. The capsule has an attached tube which passes through the
10 surface of the eye and extends outward from the eye useful for the subsequent
injection of a drug. While in the vitreous, the device is not anchored and may move
about freely.

U.S. Patent No. 5,378,475 (often referred to as Vitrasert) describes a device
15 which has been developed for insertion in the vitreous region of the eye, and is
described in T.J. Smith et al., Sustained-Release Ganciclovir, *Arch. Ophthalmol.*, 110,
255-258 (1992) and G.E. Sanborn, et al., Sustained-Release Ganciclovir Therapy for
Treatment of Cytomegalovirus Retinitis. Use of an Intravitreal Device, *Arch.
Ophthalmol.*, 110, 188-195 (1992). This device consists of an inner core of
20 pharmacologic agent surrounded by two coatings with different permeabilities. Drug
diffuses through a small opening in one of these coatings achieving near-order release
kinetics. It is implanted in the region of the pars plana through a 3.5-5.0 mm scleral
incision. The implant must be removed and replaced every 6 months in the operating
room as the drug becomes depleted. There is an approximately 25% complication
25 rate from these procedures. The device is membrane diffusion drug delivery system
that relies on EVA/PVA polymers to mediate release rate. Thus, many agents cannot
be effectively delivered from such a system because their permeation rate through the
rate controlling material of the system is too small to produce a useful effect. Other
agents cannot be satisfactorily delivered by diffusional devices because of a particular
30 chemical characteristic of the agent. This includes salts, because of their ionic
character, and unstable polar compounds that cannot be formulated into a composition
suitable for storage and delivery from such systems.

U.S. Patent No. 5,098,443 describes a series of C-shaped rings that are inserted through incisions made in the eye wall or sutured around the globe of the eye. These rings may be formed from biodegradable polymers containing microparticles of drug. Alternatively, the implant may be in the form of a hollow flexible polymeric 5 cocoon with the drug disposed therewithin for slow release by osmosis. No anchoring device is described.

U.S. Patent No. 5,466,233 describes a tack for intraocular drug delivery. This device has an end that is positioned in the vitreous cavity while the head remains 10 external to the eye and abuts the scleral surface. The drug is contained in the vitreous end of the device and could be contained within a biodegradable or nonbiodegradable scaffold. Alternatively, the device may have a hollow core filled with a drug that could diffuse through the wall of the tack into the eye. This core could be refillable. The head of the tack may further have a suture hole for anchoring the sclera.

15

While intraocular devices exist which allow delivery of therapeutic agents to the eye, a need still remains for a device which accomplishes controlled, sustained 20 delivery to the posterior chamber, is implantable and removable without requiring long full thickness scleral incisions, does not cause undue patient irritation or discomfort, is stable within the vitreous region of the eye, is refillable and dose titratable, and is capable of delivering a wide range of small molecule, gene and protein therapeutics.

SUMMARY OF THE INVENTION

25 The present invention provides a delivery device and methods of use. More particularly, the present invention relates to a sustained release delivery device that is minimally invasive and refillable. The delivery device of the present invention is particularly suitable for the delivery of therapeutic agents to the posterior chamber of the eye and other limited access regions.

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An exemplary embodiment of the delivery device includes a reservoir having an inlet port at its proximal end for insertion of the agent. A scleral hub, or similar fixation element, may further be located near the proximal end for suturing or

otherwise securing the device at a desired location. The agent inserted into the reservoir through the inlet port is delivered to a treatment area by a delivery mechanism located along the reservoir and/or at the distal end of the reservoir. For example, in one embodiment, the agent may be delivered through the reservoir by, for example, forming the reservoir of a material that is permeable to the agent or, for example, providing one or more apertures in the reservoir through which the agent may flow. In another embodiment, the delivery mechanism is located at the distal end of the reservoir by, for example, forming the distal end of the reservoir of a semi-permeable membrane or providing one or more apertures in the distal end of the reservoir. The reservoir is preferably fabricated of a pliable material that allows the reservoir to be compressed for insertion through a small incision. Once inside the incision, the reservoir may automatically unfold and/or as agent is injected through the inlet port, the reservoir may unfold as it is filled with the agent.

The drug delivery device may further include a hollow body or tube inside the reservoir, wherein the proximal end of the hollow body or tube forms the inlet port. In this embodiment, hollow body or tube may provide structural rigidity that facilitates insertion of the device through a small incision. The reservoir covers at least a portion of the length of the hollow body or tube and is preferably pliable so that it may be folded, rolled and/or compressed about the hollow body or tube to enable insertion of the device through a small incision not much larger than the size of the hollow body or tube. At least one aperture in the hollow body or tube provides communication between the contents of the hollow body or tube and the reservoir such that, as the agent is inserted through the inlet port, it travels through the hollow body or tube, through the aperture(s) and into the reservoir. As the agent fills the reservoir, the reservoir unfolds. In one embodiment, the distal end of the hollow body or tube extends outside the reservoir and forms a delivery port through which the agent is delivered to the patient. In another embodiment, the therapeutic agent is delivered to the patient through the reservoir by, for example, forming the reservoir of a material that is permeable to the agent or, for example, providing one or more apertures in the reservoir through which agent may flow. A scleral hub, or similar fixation element, may further be located near the proximal end of the hollow body or tube for suturing or otherwise securing the device at a desired location.

Methods for the delivery of an agent are also disclosed. In particular, the methods involve delivery of agents to the eye to treat a variety of ocular conditions such as, for example, retinal detachment, vascular occlusions, proliferative 5 retinopathy, diabetic retinopathy, inflammations such as uveitis, choroiditis and retinitis, degenerative disease, vascular diseases and various tumors including neoplasms.

The methods comprise making a small incision in the eye to provide access to 10 the treatment site. The delivery device is provided in an "empty" state, with the reservoir empty and preferably compressed tightly as shown in Fig. 1a. Compressing the reservoir is desirable since it allows the delivery device to be passed through a small incision that requires few or no sutures for closure. The delivery device is then inserted through the incision distal end first until the scleral hub or fixation 15 mechanism abuts the incision. The scleral hub or fixation mechanism may then be sutured or secured to the sclera to assist in maintaining the device at the treatment site. Once inside the incision, the reservoir may automatically unfold. The therapeutic agent is then injected into the device through the inlet port by use of a syringe or similar mechanism containing with the agent. The agent travels into the reservoir, 20 thereby further unfolding the reservoir. Once reservoir is filled to a desired level, the syringe may be disconnected from the inlet port and the inlet port closed. The agent is then delivered to the patient either through a delivery port or through the reservoir. After delivery of the contents of the reservoir to the patient, the device may be refilled 25 for further delivery of agent or removed. At the time of removal, the reservoir is preferably empty and compressed, thereby allowing the device to be removed through a small incision that requires few or no sutures for closure.

Depending on the particular application, the device may be designed to deliver 30 a desired dose of agent at a particular rate, for example, by providing various sized reservoirs, reservoirs with various permeabilities to the agent, delivery apertures or ports with smaller or larger diameters and delivery ports with rate controlling covers.

The present delivery device and methods of use are minimally invasive. In particular, the delivery device has a small profile that allows it to be inserted through a small opening. Such an insertion procedure eliminates the risks associated with more invasive surgery, and, further, enables such procedures to take place in an office setting. Also, the device can be removed from a small insertion site, requiring few or no sutures for scleral closure. This is a dramatic improvement over state of the art technologies which require surgery for both implantation and removal.

Further, while many existing devices for ocular delivery incorporate the therapeutic agent into the structure of the implant for release via diffusion or bioerosion of the carrier, the delivery device of the present invention is a refillable device easily filled and refilled by injection. This feature allows the physician to easily titrate dosage to the need of the individual patient. Additionally, a single device may be used with a wide range of agents, because the present device avoids implantation of the agent into the structure of the device during the manufacturing process.

Still further, because release of the agent using the present delivery device is not necessarily membrane diffusion regulated, the present device lends itself to the delivery of agents that do not readily permeate through polymeric membranes, such as ionic drugs or proteins.

Other aspects and embodiments of the invention are discussed *infra*.

25 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1a illustrates an empty delivery device in accordance with an embodiment of the present invention.

Figure 1b illustrates the delivery device of Figure 1a holding an agent.

30

Figure 2 depicts the final location of the device of Figures 1a and 1b within the eye.

Figure 3 depicts the final location of the device within the eye in accordance with another embodiment of the present invention.

Figure 4a illustrates an empty delivery device in accordance with another 5 embodiment of the present invention.

Figure 4b illustrates the drug delivery device of Figure 4a holding an agent.

Figure 5 shows a cross-sectional schematic view of an eye illustrating one 10 technique of pulling back of the conjunctiva to provide access into the eye for insertion of the delivery device of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Referring now to the various figures of the drawing, wherein like reference 15 characters refer to like parts, there is shown various views of a delivery device 1, in accordance with the invention.

As shown in Figs. 1-3, the delivery device 1 includes a reservoir 2 having a proximal end 3 and a distal end 4. Located near the proximal end 3 of the reservoir 2 20 is an inlet port 5 for injection of a desired agent into the reservoir 1. Agent injected through the inlet port 5 is delivered to the treatment area through delivery mechanism 6.

The delivery device 1 may further include a hollow body or tube 10 housed at 25 least partially within the reservoir 2. The hollow body or tube 10 has a proximal end 11 and a distal end 12. Preferably, the proximal end 11 of the hollow body or tube 10 extends outside the reservoir 2, as shown in Figs 1-3, and serves as the inlet port 5 through which the agent is injected into the device.

30 The materials used in fabricating the reservoir 2 are not particularly limited, provided these materials are biocompatible and preferably insoluble in the body fluids and tissues that the device comes into contact with. In some embodiments, it is further preferred that the materials used in fabricating the reservoir 2 are pliable

materials that allows the reservoir 2 to be folded, rolled and/or compressed for insertion through a small incision that requires few or no sutures for closure. Once inside the incision, the reservoir 2 may automatically unfold or unroll to some extent. Additionally, as agent is injected through the inlet port 5 into the reservoir 2, the

5 reservoir 2 may unfold or unroll and expand as it is filled with the agent.

In one preferred embodiment, the reservoir 2 is in the form of a balloon and is fabricated of an elastic material. As the agent is injected into the inlet port 5, the agent passes into the expandable reservoir 2 or balloon, thereby inflating and

10 expanding the reservoir 2 or balloon. Pressure of the elastic material against the agent within the reservoir 2 provides a driving force for delivery of agent through the delivery mechanism 6. Suitable materials for use in forming an elastic reservoir are well known and may be readily determined by one of skill in the art. For example, some suitable include thin-walled nondistensible materials, such as PET, and more

15 elastomeric materials, such as polyurethane. When the reservoir 2 is fabricated of a material such as PET, flow through the delivery mechanism 6 is primarily driven by diffusion and/or intraocular pressure force. When the reservoir 2 is fabricated of a material such as polyurethane, delivery of the agent may be driven, a least in part, by the spring-like properties of the material forming the reservoir 2.

20

In one embodiment, the delivery mechanism comprises at least a portion of the reservoir 2. For example, this may be accomplished by fabricating at least a portion of the reservoir 2 of a material that is permeable to the agent. Such materials may vary depending on the particular application and the agent to be delivered and may be

25 readily determined by one of skill in the art. For example, this may be accomplished by fabricating at least a portion of the reservoir 2 of a material that is permeable to the agent. Such materials may vary depending on the particular application and the agent to be delivered and may be readily determined by one of skill in the art. By way of example, some suitable permeable materials may include polycarbonates, polyolefins,

30 polyurethanes, copolymers of acrylonitrile, copolymers of polyvinyl chloride, polyamides, polysulphones, polystyrenes, polyvinyl fluorides, polyvinyl alcohols, polyvinyl esters, polyvinyl butyrate, polyvinyl acetate, polyvinylidene chlorides, polyvinylidene fluorides, polyimides, polyisoprene, polyisobutylene, polybutadiene,

polyethylene, polyethers, polytetrafluoroethylene, polychloroethers, polymethylmethacrylate, polybutylmethacrylate, polyvinyl acetate, nylons, cellulose, gelatin, silicone rubbers and porous rubbers.

5 The particular material may be chosen to provide a particular rate of delivery of the agent, which may be readily determined by one of skill in the art. The rate of delivery of an agent may also be increased or decreased by varying the percentage of the reservoir 2 formed of the material permeable to the agent. Preferably, to provide a slower rate of delivery, the reservoir 2 may be fabricated of 50% or less permeable material. For example, the reservoir 2 may be fabricated of 1%, 5%, 10%, 20%, 30%, 10 40% or 50% of permeable material. For a faster rate of delivery, the reservoir may be fabricated of greater than 50% of permeable material. For example, the reservoir 2 may be fabricated of 51%, 55%, 60%, 70%, 80%, 90% or 100% of permeable material.

15

In another embodiment, for example, as shown in Fig. 4b, the delivery mechanism 6 comprises one or more apertures 7 in the reservoir 2 formed, for example, with a laser, hot wire, drilling device or similar mechanism. The one or more apertures 7 may be located along the length of the reservoir 2 and/or at the distal 20 end 4 of the reservoir 2. The number and size of the one or more apertures 7 may vary depending on the desired rate of delivery of the agent and may be readily determined by one of skill in the art.

When the delivery device 1 includes a hollow body or tube 10, the distal end 25 12 of the hollow body or tube 10 may extend outside the reservoir 2, as shown in Figs. 1-3, and may serve as the delivery mechanism 6 through which the agent is delivered to the treatment site. In this embodiment, one or more apertures 13 are located through the wall of the hollow body or tube 10 to provide communication 30 between the contents of the hollow body or tube 10 and the reservoir 2. Thus, as the agent is injected through the proximal end 11 of the hollow body or tube 10, which forms the inlet port 5, the agent flows through the hollow body or tube 10 and into the reservoir 2 through the one or more apertures 13 in the wall of the hollow body or tube 10. Preferably, the device 1 is designed such that as the agent is injected into the

delivery device 1, all or a majority of the agent injected through the inlet port 5 passes through the hollow body or tube 10 into the reservoir 2 rather than passing directly out of the device through the distal end of the hollow body or tube 10. This may be accomplished by, for example, providing one or more apertures 13 in wall of the
5 hollow body or tube 10 that are larger than or that accommodate greater flow of agent than the delivery mechanism 6. Alternatively, a valve (not shown) or similar mechanism may be located at the delivery mechanism 6 for closing off the delivery mechanism 6 during injection of the agent.

10 In a preferred embodiment, the distal end 12 of the hollow body or tube 10 is designed to provide controlled delivery of agent from the device. This may be achieved by, for example, providing a distal end 12 with small holes and/or, for example, placing a covering or lining (not shown) over the distal end 12, wherein the covering or lining has a particular porosity to the agent or wherein the covering or
15 lining is fabricated of a diffusion or rate-limiting membrane, matrix material or similar material.

In another embodiment, wherein the distal end 12 of the hollow body or tube 10 extends outside the reservoir 2, it is also possible to design the device such that
20 both the distal end 12 and the reservoir 2 form the delivery mechanism 6. Thus, for example, the distal end 12 may be designed as set out above to deliver the agent and, for example, the reservoir 2 may be fabricated of a permeable material or one or more apertures 7 may be formed in the reservoir 2. Still further, it is possible to have the distal end 12 of the hollow body or tube 10 extend outside the reservoir 2, wherein the
25 distal end 12 is closed off and does not serve as a delivery mechanism but, rather, the reservoir 2 serves as the delivery mechanism 6 by, for example, fabricating the reservoir 2 of a permeable material or forming one or more apertures 7 in the reservoir 2.

30 In another embodiment wherein the delivery device 1 includes a hollow body or tube 10, the distal end 12 of the hollow body or tube 10 may be contained within the reservoir 2, as shown in Figs. 4a and 4b. In this embodiment, the delivery mechanism 6 may comprises at least a portion of the reservoir 2 by, for example,

forming at least a portion of the reservoir 2 or the entire reservoir 2 of a material that is permeable to the agent, or one or more apertures 7 may be fabricated in the reservoir 2 as described above. In this embodiment, the distal end 12 may have an opening through which the agent travels from the inlet port 5 into the reservoir 2. At 5 least one aperture 13 may alternatively or may also be located along the hollow body or tube 10 through which agent may travel from the inlet port 5 into the reservoir 2.

The hollow body or tube 10 is preferably rigid and provides structural support beneath the reservoir 2 for easier implantation of the device 1 through the incision. 10 As such, the hollow body or tube 10 may be formed of rigid materials including, for example, stainless steel, titanium, nitinol, polymers and other similar materials. As shown in Figs. 1-4b, the hollow body or tube 10 is preferably cylindrical in shape, with a circular cross-section. However, the shape of the hollow body or tube 10 is not limited and, for example, the hollow body or tube 10 may alternatively have, for 15 example, square, rectangular, octagonal or other cross-sectional shapes.

The reservoir 2 is bonded to the hollow body or tube 10 forming a fluid-tight seal that does not separate from the hollow body or tube 10 during use, thereby preventing leakage of agent out of the device between the hollow body or tube 10 and 20 reservoir 2. This may be accomplished by using a variety of adhesives and epoxies.

The inlet port 5 of the delivery device 1 is designed such that the needle of a syringe, or similar injection mechanism, may be inserted through the inlet port 5 and the agent housed within the syringe or injection mechanism may be injected through 25 the inlet port 5 and into the reservoir 2. The inlet port 5 preferably forms a snug seal about the needle of the syringe or injection mechanism to prevent leakage of the agent out of the inlet port around the syringe needle or injection mechanism and to provide sterile injection of agent into the delivery device 1. If desired, fittings or collars (not shown), through which a syringe needle or injection mechanism may be inserted and 30 which form a snug seal about the syringe needle or injection mechanism, may be mounted on the inlet port 5.

Upon injection of the agent into the drug delivery device 1, the needle of the syringe or the injection mechanism is removed from the inlet port 5 and the inlet port 5 sealed. This may be accomplished by providing a removable cover (not shown) on the inlet port 5 that may be removed for injection of the agent and replaced when the 5 agent has been injected. In a preferred embodiment, the inlet port 5 is composed of an injectable self-sealing material through which the needle or injection mechanism may be inserted and which seals off automatically when the needle or injection mechanism is removed. Such materials are known and include, for example, silicone rubber, silicone elastomers and polyolefin.

10

As shown in Figs. 1-4b, a fixation mechanism 8, such as, for example, a scleral hub, may further be located near the inlet port 5 to assist in stabilizing the device 1 near the delivery site. Preferably, the delivery device 1 is inserted into the incision until the fixation mechanism 8 abuts the incision. In one embodiment, as 15 shown in Figs. 1-4b, the fixation mechanism 8 is in the form of extensions from the proximal end 11 of the hollow body or tube 10. These extensions rest on the surface surrounding the incision, as shown in Figs. 2-3. These extensions may be of any shape, for example, circular, rectangular, triangular, etc. and are sized to provide a surface on which the device 1 stably rests and to provide a portion that may be sutured 20 or otherwise secured to the surface surrounding the incision. While the extensions are shown as extending approximately perpendicularly from the hollow body of tube 10, the extensions are not limited to such an arrangement and may, for example, be curved away from the device so as to conform to the curvature in the surface of the eye. The overall shape and size of the fixation mechanism 8 is not limited as long as 25 irritation and damage to the surface of the eye or other area of the body that it is in contact with are minimized.

As shown in Fig. 3, the delivery device 1 may further include a tube 14 having a first end 16 and a second end 18, for the delivery of therapeutic agent directly to a 30 target site. For example, the first end 16 of the tube 14 may be connected to the distal end 4 of the reservoir 2 or the distal end 12 of the hollow body or tube 10 and the second end 18 of the tube may be secured to or located proximal to the target site (e.g. the choroids and retinal pigment epithelial cells). The tube 14 may be sized as so as

to limit delivery rate, to minimize trauma to the retina, and to minimize leaking of the agent. The tube 14 is preferably fabricated of a flexible material so that small movements of the delivery device 1 will not be translated to the retina, thereby minimizing the risk of retinal tearing, detachment and other damage.

5

In some embodiments, it may also be desirable to deliver the agent through both the reservoir 2 and the tube 14. In such embodiments, for example, in addition to a tube 14 extending from the distal end 4 of the reservoir 2 or the distal end 12 of the hollow body or tube 10, at least a portion of the reservoir 2 may be fabricated of a 10 material permeable to the agent or the reservoir 2 may have one or more apertures 7 through which the agent may be delivered from the reservoir 2 as discussed above.

The dimensions of the delivery device 1 will depend on the intended application of the device, and will be readily apparent to those having ordinary skill in 15 the art. By way of example, when the delivery device 1 is used to deliver therapeutic agents to the eye, the device is designed for insertion through a small incision, preferably ranging from about 0.25 mm to about 1 mm in diameter, more preferably less than 0.5 mm in diameter, thereby requiring few or no sutures for scleral closure at the conclusion of the procedure. As such, the cross-section of the device 1 with the 20 reservoir 2 compressed preferably ranges from about 0.25 mm to about 1 mm in diameter, and, more preferably, is no greater than 0.5 mm. Preferably, the hollow body or tube 10 has diameter ranging from about 0.5 to about 1.0 mm, and the reservoir 2 may be compressed to the hollow body or tube 10 so as to provide an overall cross section no greater than 1.0 mm. If the hollow body or tube 10 is not 25 tubular, the largest dimension of the cross section can be used to approximate the diameter for this purpose. When used to deliver agents to the posterior chamber of the eye, the device 1 preferably has a length ranging from about 0.5 cm to about 1.5 cm such that when the fixation mechanism 8 is sutured or otherwise secured to the sclera in the region of the pars plana, the delivery mechanism 6 is positioned near the 30 posterior chamber of the eye.

When included in the device 1, the dimensions of the tube 14 will depend on the intended application of the device, and will be readily apparent to those having

ordinary skill in the art. By way of example, when used to deliver an agent to the choroids and retinal pigment epithelial cells of the eye, the tube 14 is preferably sized so as to limit delivery rate, to minimize trauma to the retina, and to minimize leaking of agent. As such, the tube 14 preferably has a length ranging from about 1 cm to 5 about 2.5 cm, an outer diameter less than about 0.1 mm, and an inner diameter ranging from about 0.001 mm to about 0.007 mm, and more preferably, from about 0.005 mm to about 0.001.

The use of the delivery device 1 of the present invention can be further 10 understood from the following discussion relating to a method for treating chronic diseases of the eye by sustained release of therapeutic agent to the eye and with reference to FIGS. 1-5.

The delivery device 1 is generally used by the following procedure: the 15 delivery device 1 is prepared with the reservoir 2 empty and preferably compressed, as shown in Figs. 1a and 4a. If a hollow body or tube 10 is included in the device, the reservoir 2 is preferably compressed about the hollow body or tube 10 as shown in Fig. 1a, to provide a low profile that allows the delivery device 1 to be implanted and removed through a small access incision that requires few or no sutures for closure. If 20 a tube 14 is used for direct delivery of the therapeutic agent to the target site, the first end 16 of the tube 14 is connected to the distal end 4 of the reservoir 2 or the distal end 12 of the hollow body or tube 10.

An incision is made to provide access to the treatment site. For example, 25 when used to deliver therapeutic agent to the posterior chamber of the eye, a sclerotomy is created for insertion of the delivery device 1. Conventional techniques may be used for the creation of the sclerotomy. Such techniques require the dissection of the conjunctiva 44 and the creation of pars plana scleral incisions through the sclera 46. As shown in Fig. 5, the dissection of the conjunctiva 44 30 typically involves pulling back the conjunctiva 44 about the eye 42 so as to expose large areas of the sclera 46 and the clipping or securing of the conjunctiva 44 in that pulled back state (normal position of conjunctiva shown in phantom). In other words, the sclera 46 is not exposed only in the areas where the pars plana scleral incisions are

to be made. Surgical instruments used in the procedure are then passed through these incisions. Thus, the incisions created for the procedure must be made large enough to accommodate the instruments required for the procedure.

5 Alternatively, the creation of the sclerotomy may be accomplished by use of an alignment device and method, such as that described in U.S.S.N. 09/523,767 the teachings of which are incorporated herein by reference, that enables sutureless surgical methods and devices therefore. In particular, such methods and devices do not require the use of sutures to seal the openings through which instruments are
10 inserted. The alignment devices are inserted through the conjunctiva and sclera to form one or more entry apertures. Preferably, the alignment devices are metal or polyimide cannulas through which the surgical instruments used in the procedure are inserted into the eye.

15 The delivery device 1 is then inserted through the incision either by hand or using a variety of insertion devices, e.g. syringe-like devices, known to those of skill in the art. Once safely inside the eye, if the tube 14 is utilized in the application, microforceps or similar positioning mechanisms may be used to position the tube 14 at the treatment location.

20 The fixation mechanism 8 may then be sutured or otherwise secured to the sclera to hold the delivery device 1 in place. If a cover is used to close the inlet port 5, it is removed at this time, and, if used, a collar for providing a snug fit about the syringe or other injection mechanism is mounted on the inlet port 5. The syringe or
25 other injection mechanism is then connected to the inlet port 5 for injection of the agent into the delivery device 1. If the inlet port 5 is composed of an injectable self-sealing material through which the needle of a syringe or other injection mechanism may be inserted and which seals off automatically when the needle other injection mechanism is removed, the needle or other injection mechanism is simply inserted
30 through the inlet port 5 and the agent injected. Following injection, the conjunctiva may be adjusted to cover the distal end of the device.

When the device is used to deliver agents to the eye for the treatment of a variety of ocular conditions such as, for example, retinal detachment, occlusions, proliferative retinopathy, diabetic retinopathy, inflammations such as uveitis, choroiditis and retinitis, degenerative disease, vascular diseases and various tumors

5 including neoplasms, some agents suitable for delivery to the eye may include, for example, antibiotics such as tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, cephalexin, oxytetracycline, chloramphenicol, rifampicin, ciprofloxacin, tobramycin, gentamycin, and erythromycin and penicillin; antifungals such as amphotericin B and miconazole; antibacterials such as sulfonamides,

10 sulfadiazine, sulfacetamide, sulfamethizole and sulfisoxazole, nitrofurazone and sodium propionate; antivirals, such as idoxuridine trifluorotymidine, acyclovir, ganciclovir and interferon; antibacterial agents such as nitrofurazone and sodium propionate; antiallergenics such as sodium cromoglycate, antazoline, methapyriline, chlorpheniramine, cetirizine, pyrilamine and prophenpyridamine; anti-inflammatories

15 such as hydrocortisone, hydrocortisone acetate, dexamethasone 21-phosphate, fluocinolone, medrysone, methylprednisolone, prednisolone 21-phosphate, prednisolone acetate, fluoromethalone, betamethasone and triamcinolone; non-steroidal anti-inflammatories such as salicylate, indomethacin, ibuprofen, diclofenac, flurbiprofen and piroxicam; decongestants such as phenylephrine, naphazoline and

20 tetrahydrozoline; decongestants such as phenylephrine, naphazoline, and tetrahydrazoline; miotics and anti-cholinesterase such as pilocarpine, salicylate, carbachol, acetylcholine chloride, physostigmine, eserine, diisopropyl fluorophosphate, phospholine iodine, and demecarium bromide; mydriatics such as atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine,

25 and hydroxyamphetamine; sympathomimetics such as epinephrine; antineoplastics such as carmustine, cisplatin and fluorouracil; immunological drugs such as vaccines and immune stimulants; hormonal agents such as estrogens, estradiol, progestational, progesterone, insulin, calcitonin, parathyroid hormone and peptide and vasopressin hypothalamus releasing factor; beta adrenergic blockers such as timolol maleate,

30 levobunolol HCl and betaxolol HCl; growth factors such as epidermal growth factor, fibroblast growth factor, platelet derived growth factor, transforming growth factor beta, somatotropin and fibronectin; carbonic anhydrase inhibitors such as dichlorophenamide, acetazolamide and methazolamide; inhibitors of angiogenesis

such as angiostatin, anecortave acetate, thrombospondin, and anti-VEGF antibody; and other therapeutic agents such as prostaglandins, antiprostaglandins and prostaglandin precursors.

5 In some applications, additives may further be included in the agent and, for example, some suitable additives may include water, saline, dextrose, carriers, preservatives, stabilizing agents, wetting agents, emulsifying agents or other similar materials.

10 In one embodiment, wherein the delivery device 1 comprises a reservoir 2 having an inlet port 5 located near the proximal end 3 of the reservoir 2, the agent injected through the inlet port 5 travels into the reservoir 2. If the reservoir 2 is fabricated of an elastic material, the reservoir 2 inflates/expands as it is filled. When the agent has been injected, the needle or other injection mechanism is removed from 15 the inlet port 5 and the inlet port 5 sealed. The agent in the reservoir 2 is then delivered gradually via the delivery mechanism 6. If tube 14 is included, the agent is delivered through the tube 14 and/or reservoir 2. Once the therapeutic agent had been delivered to the treatment area, the delivery device 1 may be refilled for further delivery or removed if the required dose of agent has been delivered for treatment of 20 the condition. If required, an aspirating device or similar mechanism (not shown) may be used to further compress the reservoir 2, thereby enabling removal of the delivery device 1 through a small incision that requires few or no sutures are required for scleral closure.

25 In the embodiment that further comprises a hollow body or tube 10, the agent injected through the inlet port 5 travels through the hollow body or tube 10 and into the reservoir 2 through either the one or more apertures 13 in the hollow body or tube 10 or the distal end 12 of the hollow body or tube. The needle or other injection mechanism is then removed from the inlet port 5 and the inlet port 5 sealed. The 30 agent in the reservoir 2 is then delivered to the treatment area gradually through the reservoir 2 and/or through the distal end 12 of the hollow body or tube 10. If tube 14 is included, the agent is delivered through the tube 14 and/or reservoir 2. Once the therapeutic agent had been delivered to the treatment area, the delivery device 1 may

be refilled for further delivery or removed if the required dose of agent has been delivered for treatment of the condition. If required, an aspirating device or similar mechanism (not shown) may be used to further compress the reservoir 2 about the hollow body or tube 10, thereby enabling removal of the delivery device 1 through a 5 small incision that requires few or no sutures are required for scleral closure.

The invention is not be limited to ocular applications, and is particularly useful in other limited access regions such as the inner ear.

10 The present invention also includes kits that comprise one or more device of the invention, preferably packaged in sterile condition. Kits of the invention also may include, for example, one or more tubes 14, one or more reservoirs 2, means for suturing or securing the fixation mechanism 8 to the sclera, etc. for use with the device, preferably packaged in sterile condition, and/or written instructions for use of 15 the device and other components of the kit.

All documents mentioned herein are incorporated by reference herein in their entirety.

20 The foregoing description of the invention is merely illustrative thereof, and it is understood that variations and modifications can be effected without departing from the scope or spirit of the invention as set forth in the following claims.

What is claimed is:

1. A sustained release delivery device for delivering an agent to the interior of a patient's eye, comprising:
 - a reservoir having a proximal end and a distal end;
 - an inlet port near the proximal end of the reservoir for injection of an agent into the reservoir; and
 - a delivery mechanism for delivering the agent from the reservoir to the interior of a patient's eye at a desired rate.
2. The delivery device of claim 1, wherein the delivery mechanism comprises at least one aperture in the reservoir.
3. The delivery device of claim 2, wherein the delivery mechanism comprises a single aperture at the distal end of the reservoir.
4. The delivery device of claim 2, wherein the size and/or number of the at least one aperture in the reservoir controls the rate of delivery of the agent.
5. The delivery device of claim 2 or 3, further comprising a mechanism for controlling the rate of delivery of the agent through the at least one aperture in the reservoir.
6. The delivery device of claim 5, wherein the mechanism for controlling the rate of delivery of therapeutic agent comprises a porous lining that covers the at least one aperture in the reservoir.
7. The delivery device of claim 5, wherein the mechanism for controlling the rate of delivery of therapeutic agent comprises a matrix material, a diffusion-limiting material or rate-limiting membrane covering the at least one aperture in the reservoir.
8. The delivery device of claim 1, wherein the delivery mechanism comprises at least a portion of the reservoir, which is fabricated of a material permeable to the agent.

9. The delivery device of claim 8, wherein the percentage of the reservoir fabricated of a material permeable to the agent controls the rate of delivery of the agent.
10. The delivery device of claim 1, wherein the delivery mechanism comprises a hollow tube extending from the distal end of the reservoir.
11. The delivery device of any one of claims 1 through 10, further comprising a hub near the inlet port for securing the delivery device in place.
12. The delivery device of any one of claims 1 through 11, further comprising a hollow body at least partially housed in the reservoir.
13. The delivery device of claim 1, wherein the hollow body has a proximal end and a distal end, and the proximal end of the hollow body extends outside the reservoir and comprises the inlet port.
14. The delivery device of claim 12 or 13, wherein the distal end of the hollow body extends outside the reservoir and comprises the delivery mechanism.
15. The delivery device of claim 14 further comprising at least one aperture in a portion of the hollow body housed in the reservoir, whereby the at least one aperture provides communication between the contents of the hollow body and the contents of the reservoir.
16. The device of any one of claims 1 through 15, wherein the reservoir is fabricated of a pliable material that enables folding, rolling and/or compression of the reservoir.
17. The device of claim 16, wherein the reservoir is fabricated of an elastic material whereby the reservoir expands when filled with the agent.

18. The device of claim 17, wherein pressure of the elastic material against the agent within the reservoir provides a driving force for delivery of agent through the delivery mechanism.
19. A sustained release delivery device for delivering an agent to a patient, comprising:
 - a hollow body having a proximal end and a distal end;
 - an inlet port at the proximal end of the hollow body for injection of the agent;
 - a pliable reservoir covering at least a portion of the hollow body;
 - at least one aperture in the hollow body for providing communication between the hollow body and the reservoir;
 - a delivery mechanism for delivering the agent to the patient, the delivery mechanism in communication with the reservoir whereby therapeutic agent is injected through the inlet port and travels into the reservoir and, whereby upon closure of the inlet port, the therapeutic agent flows out of the reservoir through the delivery mechanism at a desired rate.
20. The delivery device of 19, wherein the distal end of the hollow body extends outside the reservoir and comprises the delivery mechanism.
21. The delivery device of claim 19 or 20, further comprising a mechanism for controlling the rate of delivery of the agent through the delivery mechanism.
22. The delivery device of claim 21, wherein the mechanism for controlling the rate of delivery of the agent comprises a porous lining that covers the delivery mechanism.
23. The delivery device of claim 21, wherein the mechanism for controlling the rate of delivery of the agent comprises a matrix material, a diffusion-limiting material or rate-limiting membrane covering the delivery mechanism.
24. The delivery device of claim 21, wherein the delivery mechanism comprises the distal end of the hollow body and the mechanism for controlling the rate of

delivery of the agent comprises forming a plurality of apertures in the distal end of the hollow body.

25. The delivery device of claims 24, wherein the size and/or number of the plurality of apertures in the distal end of the hollow body controls the rate of delivery of the agent.

26. The delivery device of claim 19, wherein the delivery mechanism comprises at least a portion of the reservoir, which is fabricated of a material permeable to the agent.

27. The delivery device of claim 26, wherein the percentage of the reservoir fabricated of a material permeable to the agent controls the rate of delivery of the agent.

28. The delivery device of claim 19, wherein the delivery mechanism comprises at least one aperture in the reservoir.

29. The delivery device of claim 28, wherein the delivery mechanism comprises a single aperture at the distal end of the reservoir.

30. The delivery device of claim 28, wherein the size and/or number of the at least one aperture in the reservoir controls the rate of delivery of the agent.

31. The delivery device claim 19, wherein the delivery mechanism is a hollow tube extending from the distal end of the hollow body.

32. The delivery device of any one of claims 19 through 31, further comprising a hub for securing the device at the treatment area.

33. The delivery device of any one of claims 19 through 32, wherein the hollow body is rigid.

34. The delivery device of any one of claims 19 through 33, wherein the hollow body is cylindrical in shape.
35. The delivery device of any one of claims 19 through 33, wherein the inlet port is fabricated of an injectable self-sealing material.
36. The delivery device of claim 35, wherein the injectable self-sealing material is selected from silicone rubber, silicone elastomers and polyolefin.
37. The delivery device of any one of claims 1 through 36, wherein the device may be inserted through an incision requiring few or no sutures for closure.
38. The delivery device of claim 37, wherein the largest dimension of the cross section of the empty delivery ranges from about 0.25 mm to about 1 mm.
39. The delivery device of claim 38, wherein the largest dimension of the cross section of the empty delivery ranges from about 0.25 mm to about 0.5 mm.
40. The delivery device of any one of claims 1 through 39, wherein the device has a length ranging from about 0.5 cm to about 1.5 cm.
41. The delivery device of claim 10 or 31, wherein the hollow tube has a length ranging from about 1 cm to about 2.5 cm.
42. The delivery device of any one of claims 10, 31 or 41 wherein the hollow tube has an outer diameter less than about 0.1 mm, and an inner diameter ranging from about 0.001 mm to about 0.007 mm.
43. The delivery device of claim 42, wherein the hollow tube has an inner diameter ranging from about 0.005 mm to about 0.001 mm.
44. A sustained release delivery device that utilizes the elastomeric properties of a reservoir housing an agent to deliver the agent from the reservoir to a treatment site at a desired rate.

45. A sustained release delivery device comprising
a reservoir fabricated of an elastomeric material, the reservoir having a
proximal end and a distal end;
an inlet port near the proximal end of the reservoir for injection of an agent
into the reservoir; and
a delivery mechanism for delivering the agent from the reservoir to the interior
of a patient's eye at a desired rate, whereby the delivery device utilizes the elastomeric
properties of the reservoir to deliver the agent at a desired rate.
46. A medical device kit, comprising one or more of the delivery devices of any
one of claims 1 through 45.
47. The kit of claim 46, wherein the one or more delivery devices are packaged in
sterile condition.
48. A method for sustained delivery of an agent, the method comprising the steps
of:
(a) providing a sustained release delivery device comprising:
a pliable reservoir having a proximal end and a distal end, the
reservoir being empty;
an inlet port near the proximal end of the reservoir for injection of an
agent into the reservoir; and
a delivery mechanism for delivering the agent from the reservoir to the
patient;
(b) making an incision in the patient to access the treatment area;
(c) compressing the pliable reservoir for insertion;
(d) inserting the delivery device into the treatment area through the incision
such that the inlet port remains outside the incision;
(e) using an injection mechanism to inject the agent through the inlet port;
(f) allowing the therapeutic agent to flow into the reservoir;
(g) removing the injection mechanism from the inlet port and closing off the
inlet port;

- (h) allowing the therapeutic agent to travel out of the reservoir and to the patient through the delivery mechanism;
 - (i) optionally repeating steps (c) through (h) one or more times; and
 - (j) removing the delivery device from the treatment area.
49. A method for sustained delivery of an agent, the method comprising the steps of:
- (a) providing a sustained release delivery device comprising:
 - a hollow body having a proximal end and a distal end;
 - an inlet port at the proximal end of the hollow body for injection of the agent;
 - a pliable reservoir covering at least a portion of the hollow body, the reservoir being empty;
 - at least one aperture in the hollow body for providing communication between the hollow body and the reservoir;
 - a delivery mechanism for delivering the agent in the reservoir to the patient;
 - (b) making an incision in the patient to access the treatment area;
 - (c) compressing the pliable reservoir about the hollow body for insertion;
 - (d) inserting the delivery device into the treatment area through the incision such that the inlet port remains outside the incision;
 - (e) using an injection mechanism to inject the therapeutic agent through the inlet port;
 - (f) allowing the therapeutic agent to flow through the hollow body, through the at least one aperture in the hollow body and into the reservoir;
 - (g) removing the injection mechanism from the inlet port and closing off the inlet port;
 - (h) allowing the therapeutic agent to travel out of the reservoir and to the patient through the a delivery mechanism;
 - (i) optionally repeating steps (c) through (h) one or more times; and
 - (j) removing the delivery device from the treatment area.

50. A method for sustained delivery of an agent comprising using the sustained release delivery device of any one of claims 1 through 45 by inserting the device into the treatment area through an incision, injecting therapeutic agent into the device through the inlet port to fill the reservoir, and allowing the delivery mechanism to deliver the agent to a treatment site at a desired rate.
51. A method for sustained delivery of an agent comprising utilizing the elastomeric properties of a reservoir housing the agent to deliver the agent from the reservoir to a treatment site at a desired rate.
52. A method for the treatment of ocular conditions in patients comprising utilizing the delivery device of any one of claims 1 through 45 to deliver one or more therapeutic agents to the eye of the patient.

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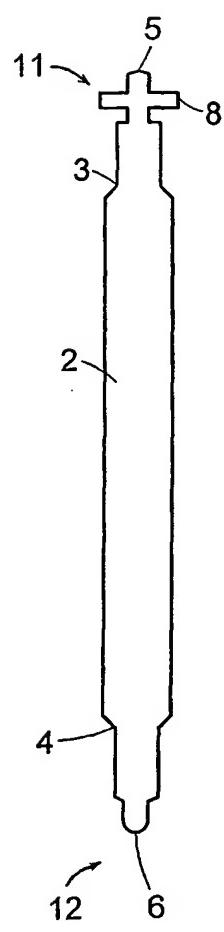


FIG. 1A

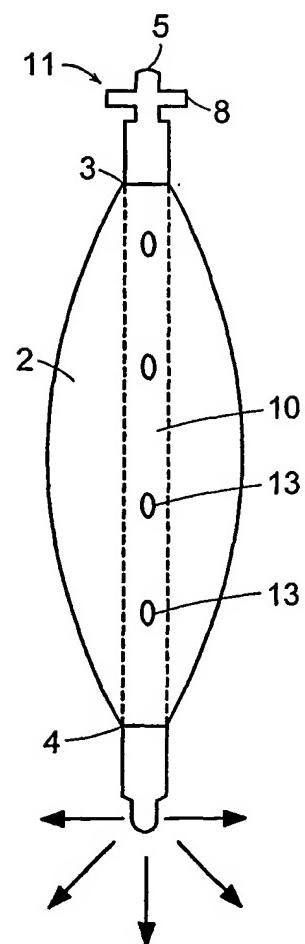


FIG. 1B

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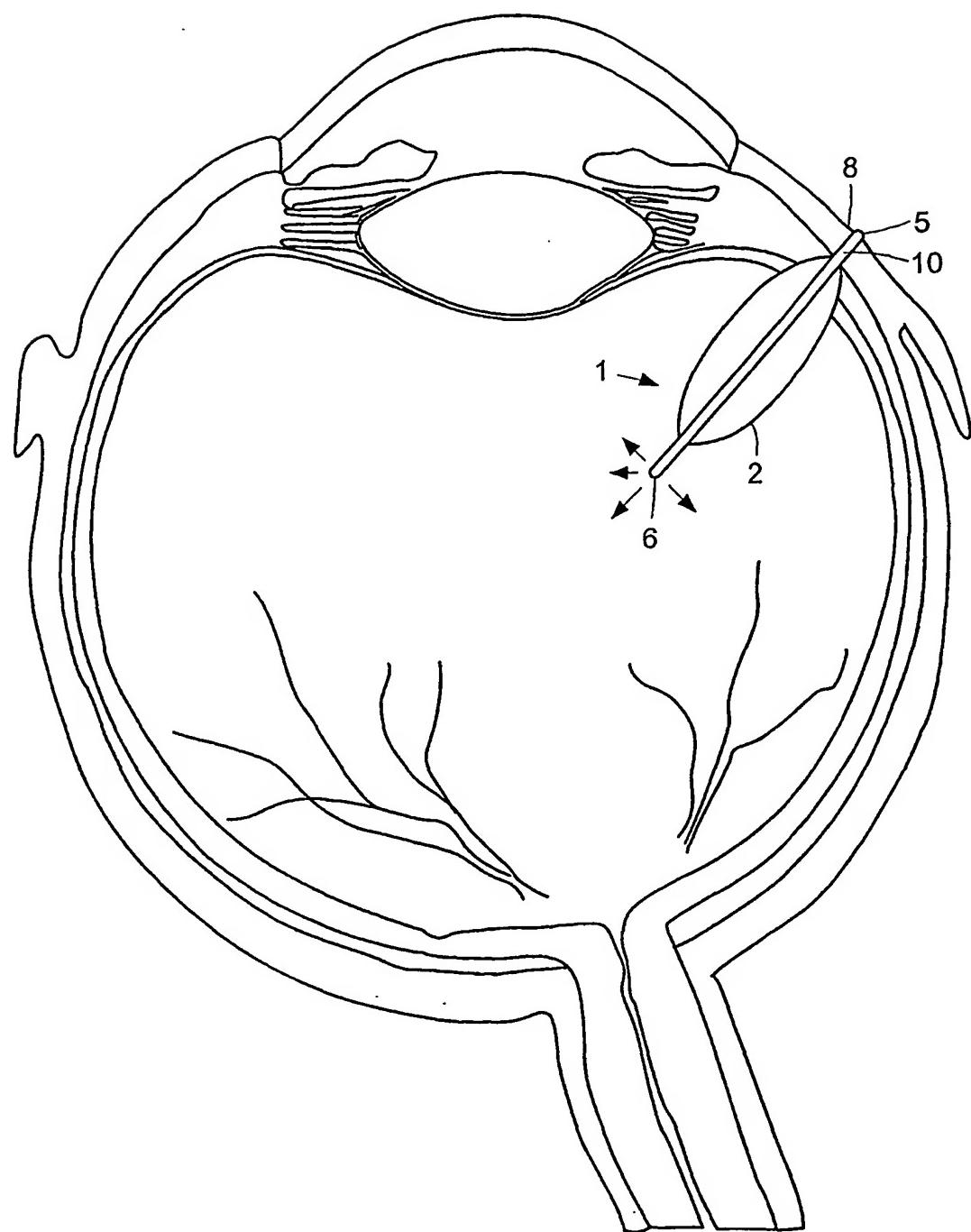


FIG. 2

SUBSTITUTE SHEET (RULE 26)

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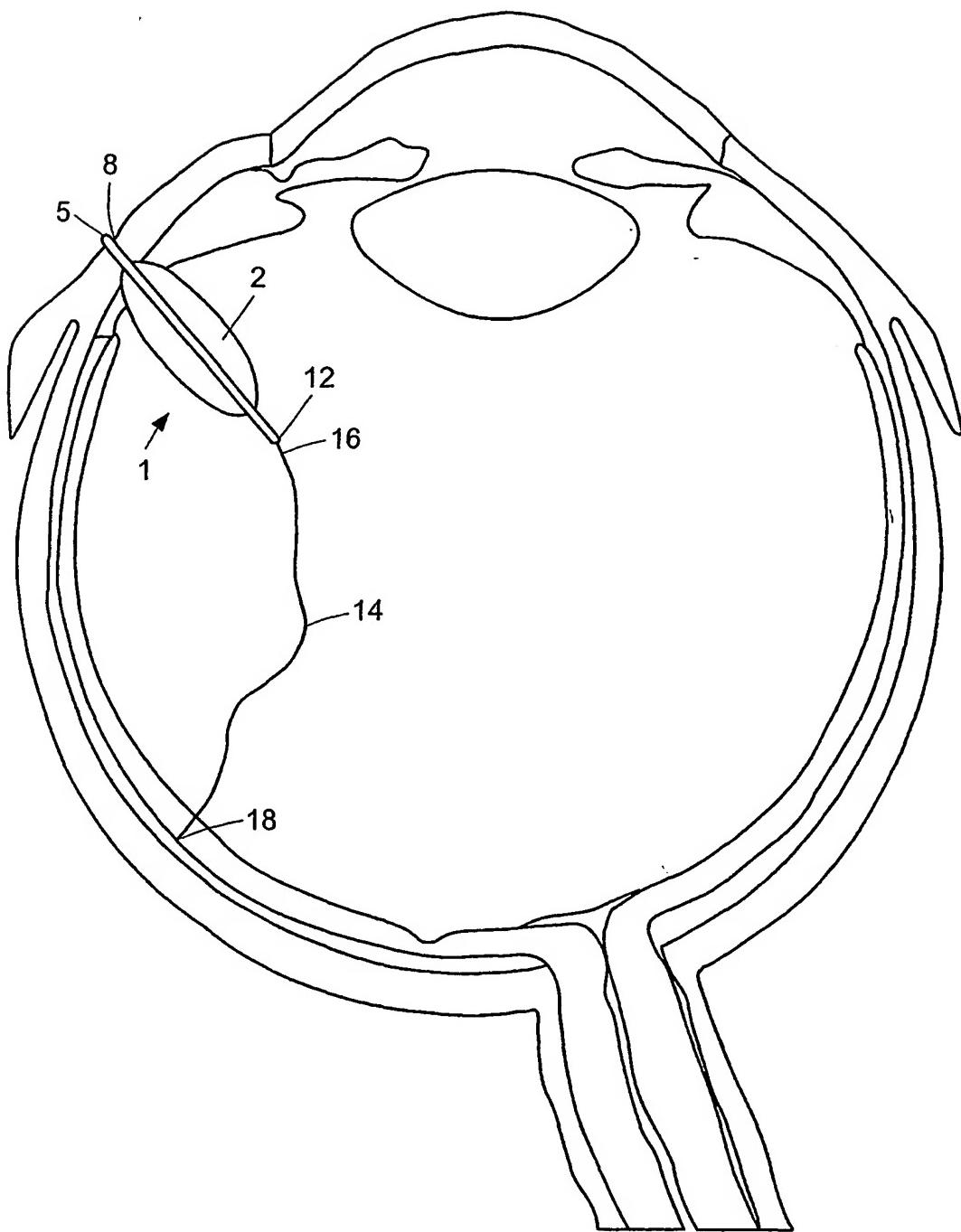


FIG. 3

SUBSTITUTE SHEET (RULE 26)

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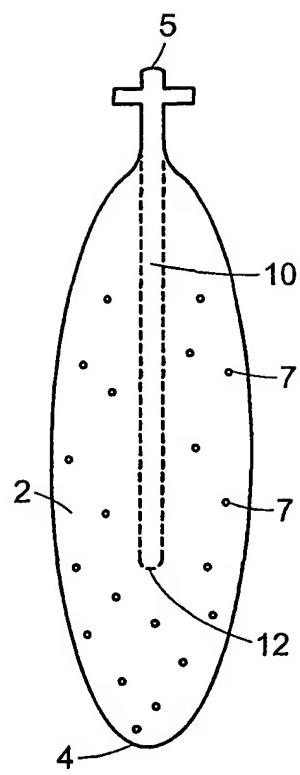
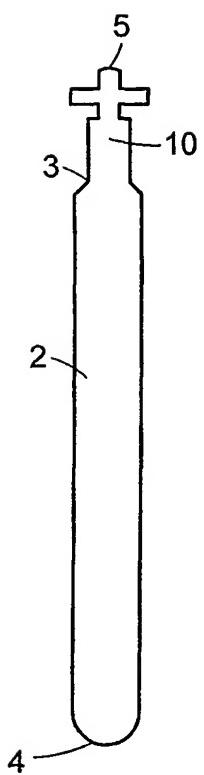


FIG. 4A

FIG. 4B

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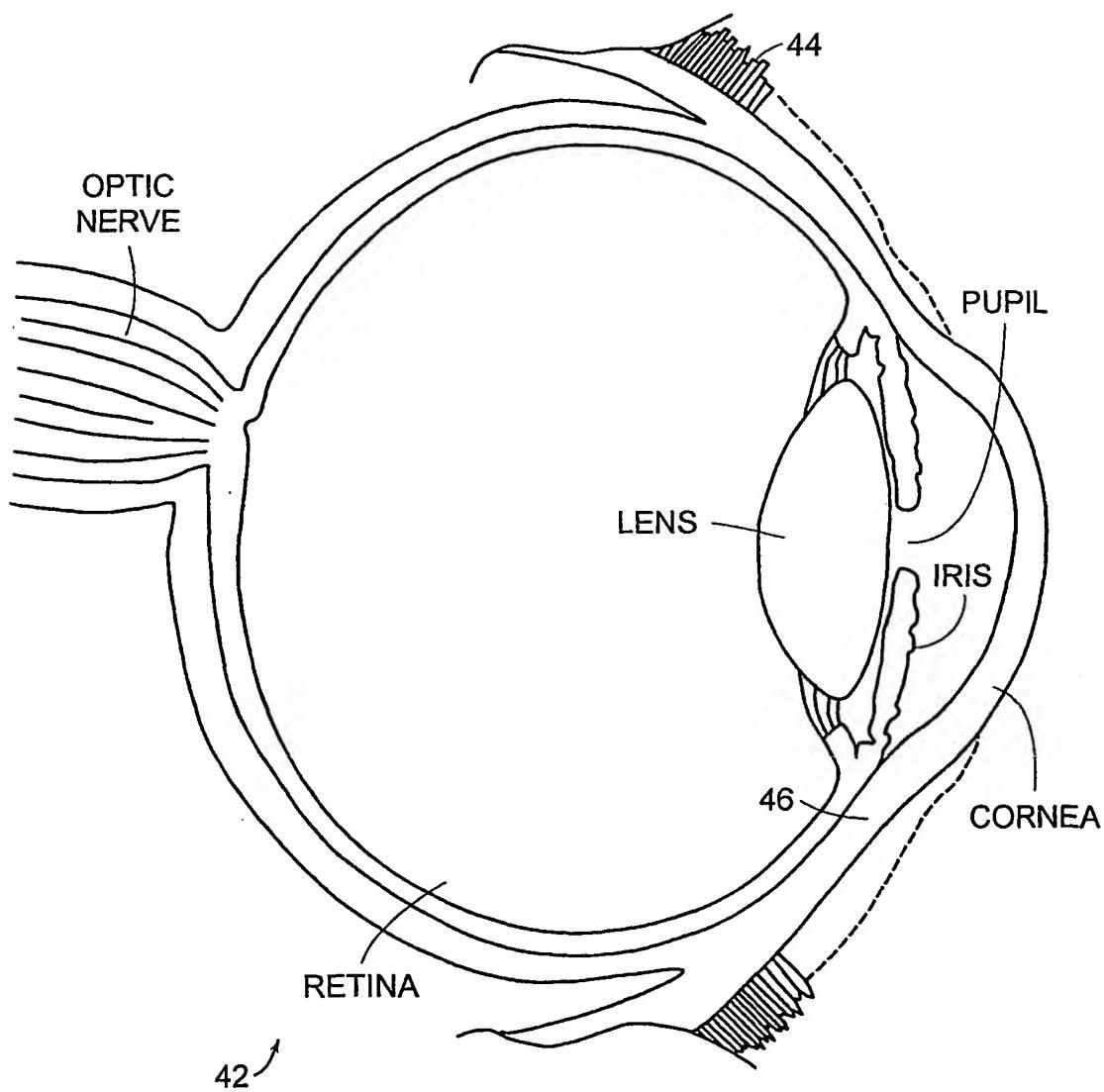


FIG. 5